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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,856	07/18/2006	Phillip Vollmers	043043-0359294	3217
27500 7590 03/23/2010 PILLSBURY WINTHROP SHAW PITTMAN LLP ATTENTION: DOCKETING DEPARTMENT P.O BOX 10500 McLean, VA 22102			EXAMINER SAOUD, CHRISTINE J	
			ART UNIT 1647	PAPER NUMBER
			MAIL DATE 03/23/2010	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/578,856	<b>Applicant(s)</b> VOLLMERS, PHILLIP	
	<b>Examiner</b> Christine J. Saoud	<b>Art Unit</b> 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 22 October 2009.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 27-32,34-43 and 48-51 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 27-32,34-43 and 48-51 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/22/09</u> . | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's response of 22 October 2009 has been received and entered. Claims 27, 31-32, 34-39, 42-43, 48-51 have been amended and claims 1-26, 33, 44-47 have been canceled. Claims 27-32, 34-43 and 48-51 are currently pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 22 October 2009 have been fully considered but are not deemed to be persuasive.

### ***Priority***

It is noted that the instant application has been filed as a 371 application of PCT/DE2004/002503. However, the instant application does not appear to obtain benefit to the PCT application because the inventorship is not the same. The inventors on PCT/DE2004/002503 is Heinz Vollmers and Hans Konrad Muller-Hermelink while the inventor of the instant application is Phillip Vollmers.

Applicant is advised that art will be applied accordingly.

Applicant has attempted to address this issue by filing a Request for change of inventorship, however, the required signatures are either missing or too faint to be seen or read.

***Inventorship***

The request to correct the inventorship of this nonprovisional application under 37 CFR 1.48(a) is deficient because:

The signature of the inventor to be added (Heinz Peter Vollmers) is missing or not legible and the signature of the inventor to be deleted (Phillip Vollmers) is not legible.

***Oath/Declaration***

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:  
The signature is not in permanent ink, or its equivalent in quality, as required under 37 CFR 1.52(a)(1)(iv).

The Examiner is viewing an electronic version of the papers which were filed. The examiner cannot determine the quality of the ink used for the signature, however, the signature is such that it cannot be viewed and is too faint to read.

***Information Disclosure Statement***

It is noted that the Examiner made a mistake regarding the 4/16/09 IDS. The IDS filed 4/16/09 was in compliance with 37 CFR 1.98(a)(1) and was considered as evidenced by the signed copy sent out with the previous Office action.

Therefore, all duplicate citations which appear in the most recently filed IDS have been lined through since the references were considered in the 4/16/09 IDS.

The Examiner previously indicated that several references were in German and no translation of the abstract and/or relevant portions were provided and that these references have only been considered in so far as the Examiner reads German. Applicant asserts that English language equivalents were submitted in an IDS for consideration and requests that the Examiner “identify which references in the German language have not been considered”.

Again, it was stated that the German references were considered in so far as the Examiner reads German. Because the Examiner is not fluent in German, the Examiner is able to identify which references have an English language equivalent. Therefore, if Applicant is aware of a reference which was submitted in German that does not have an English language equivalent and would like the abstract and/or relevant portions considered in English, then Applicant may wish to submit a translation. Applicant is not required to submit a translation – this statement was only meant as a suggestion.

### ***Specification***

The disclosure is objected to because of the following informalities:

The description of Figures 1, 2, 4 and 5 are not clear. While the specification has been amended to more accurately reflect what is described in the Figures, there are still deficiencies.

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Applicant asserts that labels on the axis for Figures 1 and 2 are not required because the description of the Figure in the specification is clear. Applicant's arguments have been fully considered, but are not found persuasive. There is no indication of units for the Y-axis which makes evaluation of the data presented therein confusing. Units of what is being measured is necessary for making a proper evaluation of the data.

Additionally, Figure 2 cannot be evaluated because there is no distinction between the kontrolle and SAM-6 as the bars of both are open. It is not clear which bar corresponds to which condition. Furthermore, the description in the specification for the X-axis does not make sense with the X-axis of the figure. The description in the Specification refers to LDL fractions being oxidized to different degrees, but the X-axis is labeled as 0, 3 and 15 hours. Therefore, the description of what is being shown in Figure 2 is not clear.

The Specification has been amended to refer to Figure 4 and 5 as showing the result of Sudan III staining. The description of Figure 4 states that the figure "shows cells that were incubated for 48 h with either SAM-6 or an IgM control antibody". However, Figure 4 is a single view - for this Figure to be a comparison, there would need to be 2 views or some distinction in color of staining. Since the figure is in black and white, it is not clear if color was intended. The description of this figure implies that there is red staining, but again, the figure is in black and white.

The amendment for reference to Figure 5 was incomplete in that the text now reads "For the stains shown in Figure 9 Figure 5". Applicant may wish to consider

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further amendment to this portion of the text as there is no Figure 9 in the instant application.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-32, 34-43 and 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling an antibody comprising SEQ ID NO:1 (VL) and SEQ ID NO:3 (VH) and/or binding fragments comprising the VL/VH and which bind to LDL or oxidized LDL, does not reasonably provide enablement for any antibody with binding specificity for the antigen and having: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or less than the full complement of VL CDR1-3 and VH CDR1-3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims for the reasons of record in the previous Office action (reproduced below).

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as broadly encompassing of an antibody or antigen binding fragment thereof with binding specificity for LDL or oxidized LDL, and where the antibody has: at least 75%, 80%, 85%, 90% or 95% identity to either the VL of SEQ ID NO:1 and/or the VH of SEQ ID NO:3, or a single VL domain (SEQ ID NO:1) or a single VH domain (SEQ ID NO:3), or a single CDR domain or less than the full complement of VL CDR1-3 and VH CDR1-3 from SEQ ID NO:1 and/or SEQ ID NO:3.

The relative skill in the art required to practice the invention is a molecular immunologist.

Disclosure in the Specification

The specification discloses a single isolated antibody, SAM-6 and sometimes called SAM-6.10, which binds LDL and oxidized LDL. At the time of filing, Applicant's specification did not reveal the structural identity of the antigen but generally characterized the antigen as LDL or oxidized LDL and the ability of the antibody to bind these LDL molecules was measured by an ELISA assay (page 14 of the specification). The sequence for the antibody (SAM-6 and/or SAM-6.10) is disclosed for VL and VH (SEQ ID NO:1 and 3, respectively). The antibody was shown to reduce LDL levels in vivo (Experiments 1 and 2, although no data is provided since the Figures which are discussed in the Specification are not present in the Application).

The specification contemplates but does not specifically disclose working embodiments for just any of the antibody structures encompassed by the claims much less that any modified antibody would have the required properties of binding LDL or oxidized LDL or complementary carbohydrate structures since no actual structure of the specific antigen is provided.

Without sufficient guidance in the written description alone, the ordinary artisan could not practice making and using the myriad antibody embodiments encompassed by the claims because the specification and claims do not define which regions and domains are subject to variation, which regions or domains could tolerate the introduction of the variation, or the nature and extent of the variation. For example, the claims are not limited to whether the extent of variation comprises amino acid substitutions, insertions, deletions and combinations thereof so that the ordinary artisan could predict which variation would not compromise antigen binding specificity. The claims are not limited as to whether the variation occurs in the antigen binding domains or Fc regions, or the CDRs and/or framework domains. Thus it is not readily apparent from the specification or the original claims as filed, how the ordinary artisan could practice the invention without incurring undue experimentation in order to identify a reasonable number of working embodiments based on the extent of antibody variation encompassed by the claims. Further, the claims encompass antibody embodiments having structures that are generally viewed in the field of art as being non-operative or at least unpredictable as to their antigen affinity, namely, antibodies having single variable domains or those having fewer than the full complement of both VL and VH CDRs. Thus the ordinary artisan could not reduce to practice the myriad embodiments and expect to obtain a reasonable number of working embodiments absent undue experimentation at the levels of gene manipulation, antibody screening and bioassay performance.



**Prior Art Status: Single CDR-domain Antibodies**

The claims encompass isolated antibodies comprising a single CDR domain (and less than the full complement of VH/VL CDRs) from SAM-6 antibody. Applicants have not shown that any isolated antibody comprising less than a full complement of VH/VL CDRs from a parent SAM-6 antibody of SEQ ID NO:1 and 3 would retain the antigen binding to the LDL and oxidized LDL tested. In fact there are numerous publications acknowledging that the conformation of CDRs as well as framework residues influence binding.

MacCallum *et al.* (J. Mol. Biol. 262:732-745 (1996)) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

de Pascalis *et al.* (Journal of Immunology 169, 3076-3084 (2002)) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (BBRC 307, 198-205, (2003)) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (J. Mol. Biol. 320, 415-428 (2002)) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al.* (Mol. Immunol. 44: 1075-1084 (2007)) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. 293, 865-881 (1999)) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. 294, 151-162 (1999)) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH CDRs and VL CDRs).

Analyzing applicants own disclosure, which while it does contemplates divergent CDR residues, the only working example is the SAM-6 antibody having heavy chain CDRs paired with complementary light chain CDRs. Additionally, the data indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no examples of mixing or matching of the light chain CDRs or heavy chain CDRs and most importantly there is no working example of placing a single CDR domain of a heavy chain and/or a light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

*Prior Art Status: Conservative Amino Acid Substitutions within CDR/FR Residues*

The claims encompass antibodies comprising VH domains, VL domains and CRDs which vary in the extent to which they resemble the corresponding domain in the parent SAM-6 antibody of SEQ ID NO:1 and 3. This variation can comprise any number and kind of amino acid substitutions. It is not well established in the art that all variable domains are amenable to modifications much less that that substitutions are for conservative amino acids. Numerous publications acknowledge that conservative substitutions would in fact change the binding ability of antibodies if not substantially reduce the affinity.

Brummell *et al.* (Biochemistry 32:1180-1187 (1993)) found that mutagenesis of the four HCDR3 contact residues for the carbohydrate antibody (Salmomella B O-polysaccharide) in no instance improved affinity but 60% of the mutants resulted in a 10-fold drop in binding constant (affinity electrophoresis value of 0.85), while still other mutants were lower (Table 1 and p. 1183, Col. 2, ¶2 to p. 1184, Col. 1, ¶1). Brummell demonstrates that no substitution retained antigen binding affinity similar to the wild type antibody despite targeted, conservative substitutions in known contact sites.

Kobayashi *et al.* (Protein Engineering 12:879-844 (1999)) discloses that a scFv for binding a DNA oligomer containing a (6-4) photoproduct with Phe or Tyr substitutions at Trp 33 retained "a large fraction of the wild-type binding affinity, while the Ala substitution diminished antigen binding" (Table 1). However, Kobayashi notes "replacing Trp 33 with Phe or Ala alters the local environment of the (6-4) photodimer

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since binding is accompanied by large fluorescence increases that are not seen with the wild-type scFv” (p. 883, Col. 2, ¶3).

Burks *et al.* (PNAS 94:412-417 (1997)) discloses scanning saturation mutagenesis of the anti-digoxin scFv (26-10) which also binds digitoxin and digoxigenin with high affinity and with 42-fold lower affinity to ouabain. 114 mutant scFvs were characterized for their affinities for digoxin, digitonin, digoxigenin and ouabain. Histogram analysis of the mutants (Figure 2) reveals that “not all residues are optimized in even high affinity antibodies such as 26-10, and that the absence of close contact with the hapten confers higher plasticity, i.e., the ability to tolerate a wider range of substitutions without compromising binding (p. 415, Col. 2, ¶4- p. 416, ¶1).

Brummell *et al.*, Kobayashi *et al.* and Burks *et al.* introduced conservative amino acid substitutions into CDRs to examine binding effects and demonstrate that any conservative substitution within any CDR cannot be made without affecting binding.

Jang *et al.* (Molec. Immunol. 35:1207-1217 (1998)) teach that single amino acid mutations to the CDRH3 of a scFv derived from 2C10, an anti-dsDNA autoantibody, reduced the binding activity about 20-50% compared to the unmutated scFv (Table 4).

Brorson *et al.* (J. Immunol. 163:6694-6701 (1999)) teach that single amino acid substitutions to the CDRs of IgM Abs for the bacterial protein, levan, are ablated.

Coleman (Research in Immunol. 145:33-36 (1994)) teaches that single amino acid changes within the interface of an antibody-antigen complex are important and that inasmuch as the interaction can tolerate amino acid sequence substitutions, “a very conservative substitution may abolish binding” while “in another, a non-conservative substitution may have very little effect on the binding” (p. 35, Col. 1, ¶1).

*Prior Art Status for Single Variable Domain Antibodies*

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant ( $K_D$ ), dissociation and association rates ( $K_{off}$  and  $K_{on}$  respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine,"

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or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

### ***Response to Arguments***

Applicant argues at page 12 of the response that the proper standard for enablement is whether one skilled in the art could make and use the invention without undue experimentation and that the claims are analogous to Wands, where the court held that screening hybridomas to determine those that produced monoclonal antibodies having a particular binding characteristic did not require undue experimentation. Applicant’s arguments have been fully considered, but are not found persuasive.

The production techniques involved in making the claimed antibodies comprising any variation of the antibody variable domains and retaining the binding characteristics for the antigen of interest and common to the specifically produced antibody of SEQ ID NO:1 and 3, are not even remotely related to the production techniques involved in making and screening the monoclonal antibodies of Wands' invention. In Wands, the antibody production and screening of the monoclonal antibodies occurred prior to 1981. The technology used by Wands involved generating a panel of highly specific IgM Mabs against a single known antigen, HbsAg. In 1981, Wands did not even contemplate systems for calculating a) variable domain modifications, and b) amino acid frequency alignment, much less the technology to produce recombinant antibodies as instantly claimed. Wands’ only assay for screening the monoclonal antibodies was a

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commercially available radioimmunoassay kit, and further screening to select IgM isotype and binding affinity constant for the monoclonal antibodies. This is in distinct contrast to the instantly claimed antibodies. The SAM-6.10 antibody of the instant application has the amino acid sequence of SEQ ID NO:1 and 3 (heavy and light chains). The antigen to which this defined antibody binds is not described in the specification. The specification teaches that this antibody binds to LDL cholesterol or oxidized LDL cholesterol and the instant claims are directed to variant antibodies which also bind LDL cholesterol and oxidized LDL cholesterol. This is in no way similar to the invention and methods of Wands which provided a reproducible method to arrive at the claimed invention. In the instant situation, the antigen to which the disclosed antibody was raised is not provided, nor is there a reproducible method for making the disclosed antibody. Therefore, one cannot follow the methods provided in the instant specification or even the methods in Wands to arrive at the claimed invention and the fact pattern in Wands is not the same as that in the instant application.

Further, Applicant has ignored the Wands Court discussion of what constitutes a "reasonable" number of working embodiments. Wands does not provide any guidance as to what a reasonable number of working examples should be and Applicant's reliance on the Wands decision in the instant case does not appear to appreciate any of the techniques required to produce the instantly claimed antibodies at the time the application was filed. Because the antigen to which the antibody of SEQ ID NO:1 and 3 was raised is unknown, because the molecule to which the antibody of SEQ ID NO:1 and 3 is variable and because the methods which are required to produce variants of an

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antibody are unpredictable and not disclosed, the experimentation required to make the claimed molecules would be undue and not routine as alleged by Applicant.

Applicant asserts at page 12 of the response that claims where no antibody has ever been produced are routinely granted by the Patent Office, therefore knowledge of antibody structure or predicting the effects of particular variations on antibody binding is not required to satisfy the enablement requirement. Applicant's argument has been fully considered, but is not found persuasive. First, the Examiner is not permitted to comment on the prosecution in other patent applications. Second, Applicant has not provided a single example of any such antibody patent issued by the Office and to which they have privileged access to the prosecution proceeding in order to advance the assertion that claims to any modified antibody are enabled. Such an assertion with no evidence is purely argumentative.

Applicant argues at page 13 of the response that the Patent Office cannot insist that Applicants demonstrate enablement by a particular methodology. Applicant's argument has been fully considered, but is not found persuasive. The rejection is one of lack of enablement and one of the considerations for enablement is predictability in the art. The art is highly unpredictable and the teachings in the instant specification and the prior art do not make up for this deficiency. The specification provides no direction or guidance regarding how to produce the genus of antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Furthermore, while the level of skill required to generate the antibodies is that of a

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molecular immunologist, the ordinary artisan would have been required to identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant ( $K_D$ ), dissociation and association rates ( $K_{off}$  and  $K_{on}$  respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of the antibody. The technology to perform these experiments was available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* substituted antibody clone having retained the antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))).

At page x of the response, Applicant argues that Exhibit A (Boder et al. Proc. Nat'l Acad. Sci. USA 97: 10701, 2000) describes directed evolution of scFV fragments and generation of a large number of Fv sequences with improved binding affinity



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compared to non-mutagenized antibody. Applicant's argument has been fully considered, but is not found persuasive. In Boder, a single known parent antibody against a known antigen was mutagenized and assayed for binding. Here the skilled artisan would be required to test numerous and indefinite numbers of antigens as not all HDL and LDL is the same in order to find an antigen to which both the purified and disclosed antibody could bind as well as finding an antibody which has the required amino acid sequence similarity that is being claimed. The unduly burdensome amount of experimentation to screen all possible antigens and antibodies and characterize these antibodies would not fall within what Wands considers routine experimentation.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(f) he did not himself invent the subject matter sought to be patented.

Claims 27-43 and 48-51 remain rejected under 35 U.S.C. 102(b) as being anticipated by EP 1 531 162 A1 (Vollmers et al., May 18, 2005) for the reasons of record in the previous Office action.

Vollmers (Heinz) et al. teach an antibody which is identical to that of SEQ ID NO:1 and 3 of the instant application. Therefore, the reference anticipates the instant claims.

Applicant argues that the inventorship has been changed in the instant application, and therefore, the rejection is avoided. Applicant's argument is not persuasive because the correction of inventorship lacked the proper signatures and no correction has been made.

Claims 27-43 and 48-51 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The instant application claims benefit to a PCT application DE2004/002503 for which the Applicant is Heinz Vollmers. The inventor on the instant application is Phillip Vollmers (also spelled Philip on some of the application papers). Therefore, it would appear that the applicant did not invent the claimed subject matter.

Applicant again argues that the inventorship has been changed in the instant application, and therefore, the rejection is avoided. Applicant's argument is not persuasive because the correction of inventorship lacked the proper signatures and no correction has been made.

### ***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/

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